

## REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated September 6, 2006 (hereinafter, the "Office Action"). Applicants also extend their gratitude to the Examiner for the telephonic interview conducted on August 29, 2006 with co-inventor, Dr. George Sigounas, and Applicants' representative, Shawna Cannon Lemon and the further telephonic interview conducted on November 27, 2006 with the Applicants' representative as previously identified. During the interviews, issues and rejections of record were discussed. During the November 27<sup>th</sup> interview, data indicating that erythropoietin administration followed by administration of mitomycin resulted in further reduction of tumor mass compared to administration of mitomycin alone was discussed. Although an agreement with respect to the claims was not reached, in view of the helpful and constructive dialog expressed during these interviews, Applicants set forth the claim amendments and remarks presented herein in support of the patentability of Claims 12, 19-21, 24-26 and 31-35.

### **I. Claim Rejections Under 35 U.S.C. §112, First Paragraph, Enablement**

Claims 12 and 31-35 remain rejected under 35 U.S.C. §112 and Claims 15, 19-20 stand rejected under 35 U.S.C. §112, first paragraph for the reasons previously set forth in the Office Action dated January 27, 2006 (Section 6, pages 5-7). *See* Office Action, page 2. In support of the enablement rejection, the Office Action asserts that "no reduction of tumor response was shown in the experiments to MTX. Further, as drawn to the broad claims 12, 31-35 and 19-20, the arguments are not found persuasive for the reasons of record because the claims are not limited to CIS, CIS derivatives or mitomycin." Office Action, page 3.

Applicants submit herewith an additional Declaration Under 37 C.F.R § 1.132 of George Sigounas, Ph.D. (hereinafter, the "Sigounas Declaration"). The Sigounas Declaration presents objective evidence demonstrating that erythropoietin (EPO) can modulate tumor response to mitomycin. More specifically, the studies described in the Sigounas Declaration show that tumor-bearing animals treated with mitomycin C alone had a 2-fold reduction of tumor mass compared to animals injected with saline. When EPO was injected sequentially first with EPO and then with mitomycin C, tumor mass was further reduced by 14%

compared to that seen in mice treated with mitomycin C alone. This result indicates that EPO can modulate tumor response to mitomycin C.

In addition to submitting the experimental data directed to studies with mitomycin, Applicants have further amended Claim 12 to recite "administration of cisplatin, carboplatin or mitomycin." Accordingly, Applicants respectfully submit that Claims 12, 19, 20 and 31-35 comply with the enablement requirement, and Applicants respectfully request that the rejection of these claims under 35 U.S.C. §112, first paragraph, as lacking enablement be withdrawn.

## **II. Claims Rejections Under 35 U.S.C. §112, First Paragraph, Written Description**

Claims 12, 15, 19-21, 24-26 and 31-35 stand rejected under 35 U.S.C. §112, first paragraph, as lacking written description. *See* Office Action, page 3. More specifically, the Office Action asserts that "[t]he limitation of administering EPO prior to initial administration of chemotherapeutic has no clear support in the specification and the claims as originally filed." Office Action, page 3.

In an effort to expedite prosecution of the present application, Applicants have further amended Claims 12 and 21 to recite that the amount of EPO is a "dosage in a range of 750 Units per kilogram to 2000 Units per kilogram." Claim 21 further recites that the amount is an "endothelial-inhibiting" amount. Support for these claim amendments can be found in the specification as originally filed, for example, the specification recites the following:

As used herein, endothelial-inhibiting amounts of EPO refer to those dosages which enhance or increase the suppression of endothelial growth which would otherwise occur due to exposure to a chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium. Alternatively, an endothelial-inhibiting amount of EPO may be defined as those dosages which decrease the numbers of viable endothelial cells following exposure to the chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium; the decreased number of viable cells is in comparison to that which would be expected in the absence of EPO.

Present Application, page 6, lines 19-31.

In the present methods, where it is desired to protect the endothelium from the endothelial damage and/or endothelial growth suppression caused by a chemotherapeutic agent, EPO is administered in an endothelial-protecting amount. Suitable endothelial-protecting dosages may range from about 100

U/kg to about 200 U/kg. In the present methods, where it is desired to enhance the endothelial damage and/or endothelial growth suppression caused by a chemotherapeutic agent, EPO is administered in an endothelial-inhibiting amount which may range from about 750 U/kg to about 2,000 U/kg.

Present Application, page 12, lines 26-37.

Thus, it is clear that an embodiment of the present invention contemplates administration of EPO in a dosage that is in a range from about 750 Units per kilogram to about 2,000 Units per kilogram, which can lead to endothelial-inhibition, and in turn, enhance the endothelial damage and/or endothelial growth suppression caused by a chemotherapeutic agent such as cisplatin, carboplatin or mitomycin as recited in the pending claims.

Applicants further direct the Examiner's attention to the Office Action dated December 28, 2004 (hereinafter, "the December Action"). In the December Action, it is acknowledged that in the cited reference, "patients are treated with 150 U/kg sc three times a week for 8 weeks." December Action, page 5. The December Action then concludes that the method of the prior art comprises the same method steps as claimed in the instant invention, that is administering erythropoietin in conjunction with cisplatin to the same population, that is patients with solid vascularized tumors at the same dosage, thus the method is anticipated because the method will inherently lead to the enhanced suppression of endothelial growth associated with the administration of cisplatin." December Action, page 5.

In view of the dosage-dependent function of EPO as described by the Applicants in the specification, and as noted above, a dosage of EPO in a range of about 750 U/kg to about 2,000 U/kg provides an endothelial inhibiting/suppression amount. The previously cited references do not describe a method of treating a solid vascularized tumor in a subject in need of such treatment, comprising administering erythropoietin prior to administration of a chemotherapeutic agent such as cisplatin, carboplatin or mitomycin, wherein erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of cisplatin, cisplatin derivative or mitomycin, wherein said amount is a dosage in a range of 750 Units per kilogram to 2000 Units per kilogram or administering EPO in an endothelial-inhibiting amount wherein the amount is a dosage in a range from about 750 Units per kilogram to about 2,000 Units per kilogram.

Applicants respectfully submit that the claim amendments and remarks presented herein place the application in condition for allowance. In the event that there are unresolved

issues in view of the claim amendments, consistent with the provisions of the Manual of Patent Examining Procedure (MPEP) § 2173.02, Applicants respectfully request the Examiner to suggest claim language to Applicant to improve the clarity or precision of the language used to amend the claims.

**III. Supplemental Information Disclosure Statement**

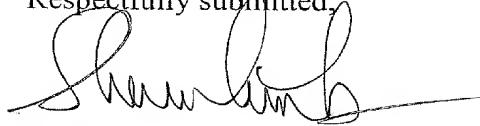
On November 29, 2006, Applicants submitted a Supplemental Information Disclosure Statement to submit references first cited in a communication presented to a foreign patent office in a counterpart foreign application not more than three (3) months prior to the filing of the Supplemental Information Disclosure Statement, and more specifically, during an Opposition Proceeding in corresponding European Patent No. 0933995 (European Patent Application No. 97940974.5). Applicants respectfully request consideration of these references, and Applicants respectfully submit that the pending claims are patentable over the cited references at least in view of the reasons set forth above and previously made of record in view of previously cited references.

**Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

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**CERTIFICATION OF TRANSMISSION  
UNDER 37 CFR § 1.8**

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